M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

5499 '00 MAR 22 A10:13

Date: February 11, 2000

To: Dockets Management Branch (HFA-305)

From: Melissa Lamb
Office of Generic Drugs

Subject: Therapeutic Equivalence of Protein Therapeutic Agents

This memorandum forwards overheads of a presentation to the Dockets Management Branch for inclusion in Docket 90S-0308. The following is information on the presentation for the Docket records:

Title of Presentation:	Therapeutic Equivalence of rhGH Based on Pharmacodynamic Endpoints
Presented for:	Preclinical and Clinical Development of Biological Therapeutics: Focus on PK and PD Annapolis, MD.
Date Presented:	10/19/99
Presented by:	Wallace P. Adams
Number of Pages:	9

Melissa Lamb

Attachment

90S-0308

M675

Therapeutic Equivalence of rhGH Based on Pharmacodynamic Endpoints

Therapeutic Equivalence of Protein Therapeutic Agents

Breakout Session C1

Preclinical and Clinical Development of Biological Therapeutics: Focus on PK and PD

Annapolis, MD

19 October 1999

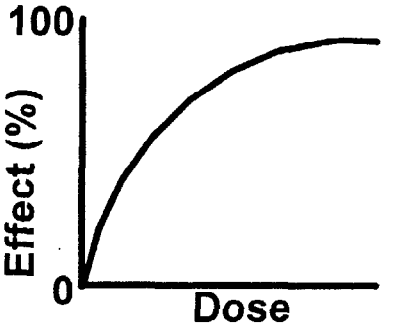
Wallace P. Adams, Ph.D.
Office of Pharmaceutical Science
CDER/FDA

E_{max} Model With Baseline Effect

$$E = E_0 + \frac{E_{max} \times Dose}{Dose + ED_{50}}$$

Where:

- **E** = **Pharmacodynamic effect**
- **E_0** = **Baseline effect (fitted)**
- **E_{max}** = **Maximum value of "E" (fitted)**
- **ED_{50}** = **Dose required to achieve 50% of E_{max}**



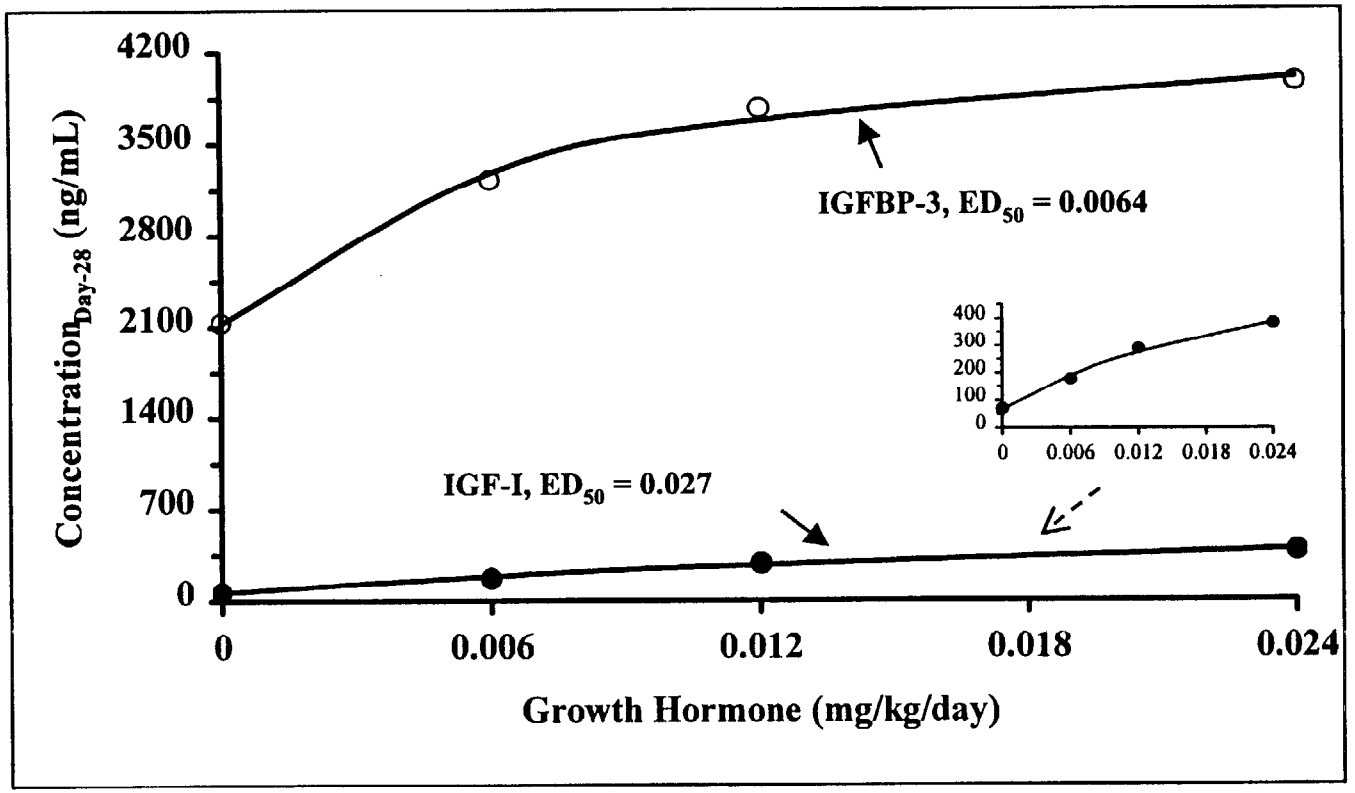
- **Predicts the maximum achievable effect**
- **Estimates the baseline effect in the absence of drug**
- **Conforms to simple theories, relating dose or concentration to receptor binding and the observed effect, which suggest that if doses or concentrations are high enough, a maximum response is achieved**

rhGH Dose-Response in GHD

(HA Wollmann et al, 1995)

- Study Design
  - 12 GHD adults (9 male, 3 female), ages 20 - 31
  - No hGH treatment within 6 months of study
  - Randomized crossover, three period
  - Daily sc injections for 4 week treatment periods
  - No washout period between treatments
  - Baseline (BL) and three doses: 0.006, 0.012, and 0.024 mg/kg/day
  - Blood samples at BL and days 7, 14, and 28
  - PD markers: serum IGF-I, IGFBP-3, bone markers

rhGH Dose-Response in GH-Deficient Adults (Observed and E_{max} model fitted)



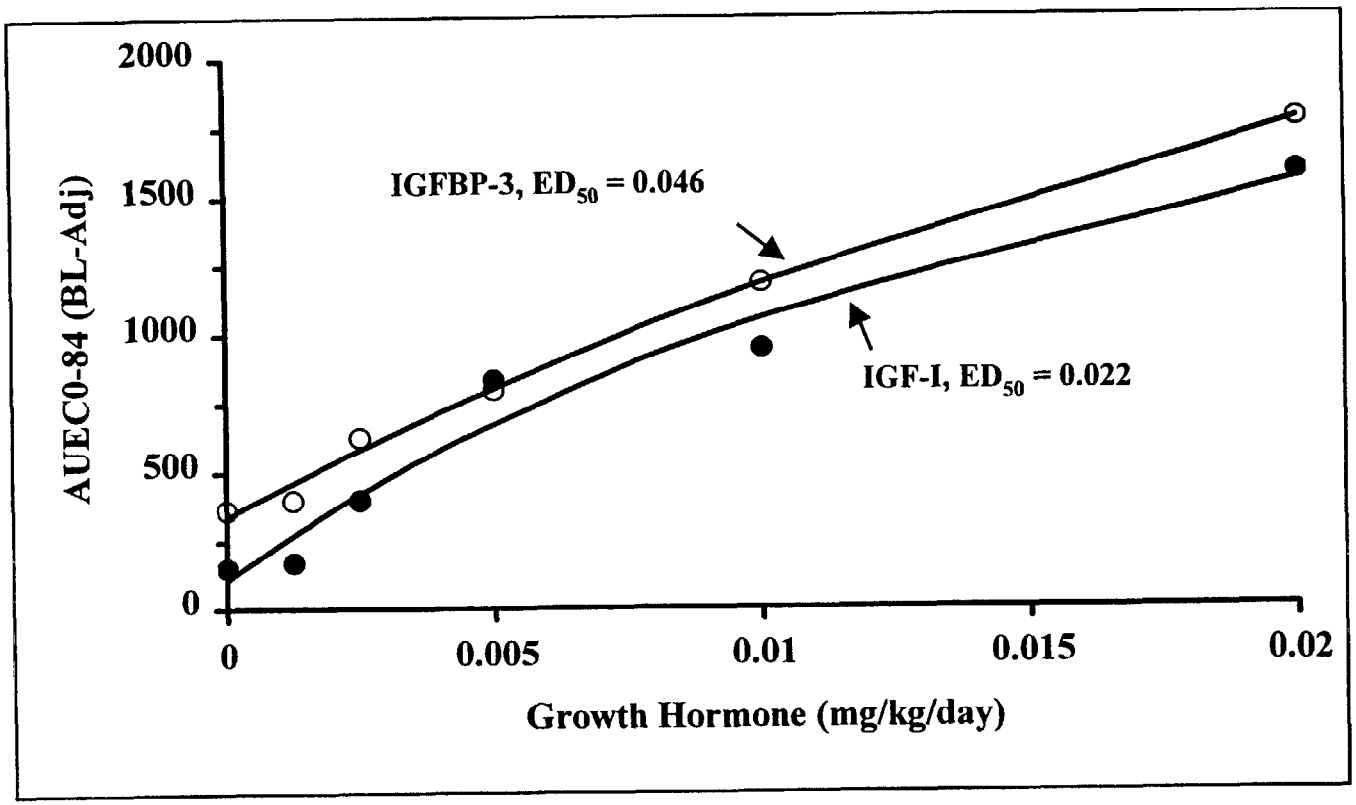
HA Wollmann et.al., Hormone Res. 1995;43:249-56

rhGH Dose-Response in Healthy Volunteers

(E Ghigo et al, 1999)

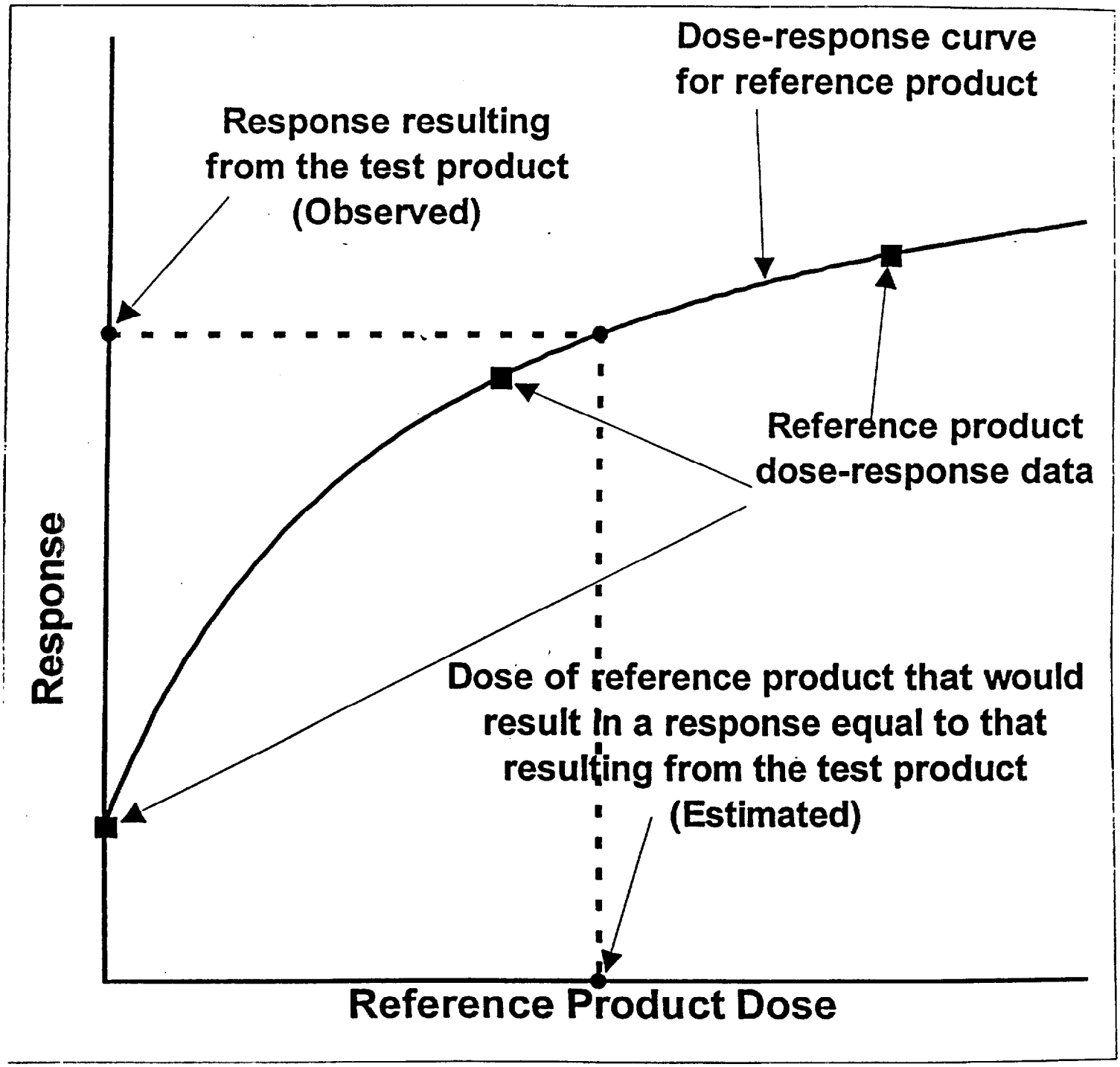
- Study Design
  - 21 healthy adults (12 male, 9 female), both groups 30.5 ± SE (2.7 ♂, 1.3 ♀) years
  - Randomized crossover, six period
  - Placebo plus 5 doses: 0.00125-0.020 mg/kg/day
  - Daily sc injections for 4 day treatment periods
  - One month washout between treatment periods
  - Blood samples at BL, at 12 hrs after each dose, and 24 hrs after 4th dose
  - PD markers: serum IGF-I, IGFBP-3

rhGH Dose-Response in Healthy Volunteers (Observed and E_{max} model fitted)



E. Ghigo et.al., Am. J. Physiol. 1999;276:E1009-13

BE Criteria on the Dose Scale: Theory



William R. Gillespie, Ph.D.
ACPS and PADAC Joint Session
16 August 1996

Dose Scale Approach

- Rationale
  - Equivalence of amount of drug that reaches the site of action (biophase) is preferred to equivalence of pharmacodynamic response
    - dose proportionality of drug concentration at biophase is assumed
    - doubling dose doubles concentration at biophase with linear pharmacokinetics
    - doubling dose does not in general double PD response
- Advantages
  - Nonlinearity on response scale eliminated
  - Relates relative amounts of drug from test and reference products delivered to the biophase

A Possible rhGH PD Study Design for Pharmaceutical Equivalence

- 36 GHD adults
- Randomized crossover 4 period
- No placebo
- 4 week treatment period with no washout between periods
- Daily sc injections for 4 weeks:
  - Reference product: 0.010, 0.020, 0.040 mg/kg/day
  - Test product: 0.010 mg/kg/day
- PD markers:
  - IGF-I (pivotal); IGFBP-3 (confirmatory) at day 28
- Blood samples: BL prior to first period and after day 28
- Conduct pilot study to estimate number of subjects and ED_{50}